EVEREST-I
Evaluation of Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter in the Treatment of Moderate-to-Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

Statistical Analysis Plan (SAP)

PR1051-002, Rev. A

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1 INTRODUCTION

This document outlines the detailed statistical methods for the data collected within the scope of Protocol # PR1051 EVEREST-I Study Revision 3.0. The purpose of this plan is to provide a framework within which answers if the study objectives can be achieved via statistically appropriate analytical methods. Specifically, the SAP serves to prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analyses in the medical industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

If a future protocol revision necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly. Amendments to this document will be finalized prior to database lock (DBL).

2 STUDY OBJECTIVE(S)

The objectives of the study are to evaluate the safety and efficacy of the Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter System in the treatment of BPH:

- To assess the efficacy of the Optilume BPH Prostatic DCB Dilation Catheter System to alleviate LUTS believed to be secondary to BPH (LUTS/BPH)
- To evaluate the safety of the Optilume BPH Prostatic DCB Dilation Catheter System in the treatment of LUTS/BPH.

3 STUDY DESIGN

This is a prospective, single arm, multi-center, open label, non-randomized study focusing on male subjects with BPH.

Subjects will be followed up post-treatment at foley removal, 2 weeks, 30 days, 90 days, 180 days and 365 days, and then annually for up to 5 years or until study close, whichever comes first. The annual follow-up after the first year is optional. A subset of the subjects will be included in the PK study cohort which includes extra follow-up visits at 1 day and 4 days post-treatment. Scheduled visits are listed in Table 5 in the protocol.

All subjects will be treated with a pre-dilation balloon and a drug-coated balloon (DCB) according to the EVEREST-I Protocol #PR1051.

3.1 STUDY ENDPOINTS

3.1.1 Primary Efficacy Endpoint: Change in IPSS score at 3 months

Improvement in International Prostate Symptom Score (IPSS) at 3 months is measured by baseline score minus 3 months score. The percent of improvement is calculated as the improvement in IPSS divided by the baseline score. A therapeutic responder is defined as a subject who has an IPSS improvement of ≥ 40%. The primary efficacy endpoint is the proportion of therapeutic responders at 3 months.

3.1.2 Primary Safety Endpoint: Major device or procedure related complications at 3 months

A major device related complication is defined as any of the following device or procedure related serious adverse events at 3 months.

- Device or procedure related new onset severe urinary retention lasting > 14 consecutive days post-healing
- Device or procedure related unresolved new onset stress urinary incontinence by 90 days
- Device or procedure related bleeding requiring transfusion

3.1.6 Exploratory Endpoints

- Change in IPSS
- Change in Qmax (Peak Urinary Flow Rate)
- Change in BPH-II (BPH Impact Index)
- Change in pain score
- Change in IIEF (International Index of Erectile Function)
- Change in EQ-5D quality of life
- Subject satisfaction
- Procedure parameters
- Change in MSHQ-EjD (Men's Sexual Health Questionnaire – Ejaculatory Dysfunction)

4 SAMPLE SIZE

Sample size calculation is based on the following assumptions:

- One-sided alpha = 5%
- Power = 80%
- Target performance goal = 50%
- Anticipated responder rate at 3 months = 70%

Under an exact, one-sided test for a single binomial proportion, at the 0.05 significance level, a sample size of 42 subjects will be required to provide at least 80% power to meet this target primary efficacy goal of 50% given the anticipated rate of 70%. With 5-10% lost to follow up, a minimum of 45 subjects will be required in this study.

5 ANALYSIS SETS

Intent-to-Treat (ITT): the ITT set will be comprised of all subjects who have provided informed consent and meet all the inclusion and none of the exclusion criteria.

Modified Intent-to-Treat (mITT): all ITT subjects who have the investigational device attempted.

Per-Protocol (PP): the PP set will be comprised of all subjects in the ITT set who have no major protocol deviations. All major protocol deviations will be reviewed and finalized before the data lock for final analysis.

The primary analysis for efficacy and safety will be based on a modified intent-to-treat principle. The per-protocol analysis set is designated as supportive.

6 STATISTICAL METHODS OF ANALYSES

6.1 GENERAL CONSIDERATIONS

The data from the study will be tabulated using descriptive analyses. In general, categorical variables will be summarized with the number and percent of subjects with the characteristic. Quantitative variables will be summarized with the mean, median, standard deviation, minimum value and maximum value.

Descriptive analyses of all adverse events (AEs) and urinary symptoms will be provided in the report. In addition, the report will include tabulated results of study deviations and device malfunctions.

6.2 BASELINE CHARACTERISTICS

Baseline characteristics will be summarized using the mean, standard deviation, median and range for continuous characteristics and using counts and percentages for categorical characteristics.

6.3 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary efficacy endpoint is the proportion of therapeutic responders defined as a subject who has an IPSS improvement of $\geq 40\%$ at 3 months. The performance goal is defined as $\geq 50\%$ responders at 3 months.

The statistical hypothesis for the primary efficacy endpoint is:

H_0: $p \leq 0.50$
Ha: $p > 0.50$

The analysis of the primary efficacy endpoint will be performed in the mITT analysis set. The primary efficacy endpoint will be assessed by calculating the proportion of subjects who have improved IPSS by 40% or more at 3 months aggregated over the mITT subjects. A 95% one-sided confidence interval (i.e., 90% two-sided confidence interval) will be estimated using the Clopper-Pearson interval (F-distribution method). In this analysis, the denominator includes all subjects in the mITT set. Subjects who have exited the study prematurely before 3 months will be assumed as a non-responder. Subjects with a missing IPSS value at 3 months will have success carried backward if the IPSS at 6 months is shown as a responder. If the lower bound of this 95% confidence interval is greater than to the performance goal of 50%, we can conclude the primary efficacy objective is met.

As a supportive analysis, the primary efficacy endpoint will also be analyzed as a continuous score for the improvement in IPSS at 3 months.

The improvement in IPSS at 3 months is calculated as baseline score minus 3 months score. Summary statistics including n, mean, SD, median, Q1 and Q3 for the improvement score will be calculated. The 95% confidence interval for the mean improvement will be calculated using an asymptotic approach.

The analyses will also be conducted in the PP set as a supportive analysis.

6.4 Analysis of Primary Safety Endpoint

The primary safety endpoint, major device or procedure-related complications as defined in the section 3.1.2, will be analyzed in the mITT set. The number and percentage of subjects experiencing at least one major device or procedure-related complication will be calculated, along with the 95% confidence interval.

Each component of the primary safety endpoint will be also analyzed in the similar fashion as the aggregated primary safety endpoint in the mITT set.

6.5 Analysis of the Exploratory Endpoints

For continuous endpoint variables, change from baseline will be summarized at each post-treatment visit using descriptive statistics such as mean, median, standard deviation, minimum value and maximum value. For categorical variables, the number and percentage of subjects with the characteristic will be presented at each post-treatment visit. In addition, 95% confidence intervals will be presented where applicable.

6.6 Analysis of Safety Data

An adverse event (AE) is defined as any adverse change (i.e., de novo or preexisting condition) from the subject's baseline medical condition(s) occurring during the course of the study. For the purpose of AE documentation, the start of the course of the study is defined as any time after the treatment has been initiated. See the Protocol for further details on AE and Serious Adverse Event (SAE) classification.

Adverse experiences will be coded using a customized AE coding list based on the Medical Dictionary for Regulatory Activities (MedDRA v21.1). All AEs will be captured from the initiation of treatment through the final visit. Adverse events will be summarized by presenting:

- The number and percentage of subjects experiencing any AE
- The number and percentage of subjects experiencing any AE by System Organ Class (SOC) and Preferred Term (PT)
- The number and percentage of subjects experiencing any SAE
- The number and percentage of subjects experiencing any AE associated with study discontinuation
- The number and percentage of subjects experiencing any AE related to the study device

- The number and percentage of subjects experiencing any AE according to degree of severity

6.7 HANDLING OF MISSING DATA

Unless otherwise specified, no imputation or other substitution for missing data will be made for analysis purposes.

6.8 VISIT WINDOWS

Visit windows are assigned to visit time points as follows:

Baseline	24 Hours	Foley Removal	4 days	2 weeks	30 days	3 Months	6 and 12 Months	Annually for up to 5 years
within 30 days	± 3 hours	≥ 48 hours	± 1 day	+ 3 days	± 7 days	± 14 days	± 30 days	± 30 days

6.9 UNSCHEDULED ASSESSMENTS

Information acquired during unscheduled assessments will be included in the study listings.

7 OTHER ANALYSES

7.1 SUBJECT DISPOSITION

Subject accountability and study discontinuation will be summarized for the ITT set. Subject accountability at each protocol required visit will be summarized as the number of subjects with complete visits, missed visits, or study discontinuations prior to the visit.

All subjects who do not complete the study will be tabulated by reason for discontinuation. Additional variables summarized may include total study duration, study completion status, and the primary reason for study discontinuation.

7.2 MEDICAL HISTROY

Medical history will be summarized for the ITT Set.

7.3 POOLABILITY ACROSS INVESTIGATIONAL SITES

This study is designed and conducted as a multi-center clinical trial. Data from all the sites will be pooled. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results.

A list of variables such as baseline demographics and characteristics will be compared across sites to assess the appropriateness of pooling data from across all sites.

7.4 CHANGES IN PLANNED ANALYSIS

Deviations or changes from this SAP deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described with justification and rationale.